University of North Carolina at Chapel Hill
Consent for Storing Biological Specimens With Identifying Information

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IRB Study # 05-EPA-525 New Study # 05-2019
Consent Form Version Date: August 28, 2008

Title of Study: Respiratory effects of short-term low-level chlorine gas exposure

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What are some general things you should know about this research study?
Research studies are designed to gain scientific information that may help other people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Research with blood, tissue and/or body fluids (specimens) can help researchers understand how the human body works. Research using specimens can also answer other questions. Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat diseases. In the future, some research may help to develop new products, such as drugs.

You may refuse to allow us to have or store your specimen. If you are a patient with an illness, you do not have to be in the research study in order to receive treatment.

Details are discussed below. It is important that you understand this information so that you can make an informed choice. You will be given a copy of this consent form. You should ask the

Initial/Date _____

researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?

The purpose of this research study is to learn about the effects of short-term, low-level chlorine gas exposure in healthy adults. To do this, we will expose volunteers performing intermittent treadmill exercise both to clean air and to an atmosphere containing 0.4 ppm chlorine gas for four hours; the exposures will be separated by a minimum of 4 weeks. This level of chlorine gas exposure is within workday limits recommended by the United States Occupational Safety and Health Administration, the National Institute of Occupational Safety and Health, and the American Conference of Governmental Industrial Hygienists. To study the effects of the chlorine exposure we will 1) evaluate changes in blood assays, 2) examine for evidence of respiratory tract inflammation and markers of oxidative stress in bronchoalveolar lavage fluid and nasal lavage fluid, and 3) obtain exhaled breath condensate to analyze for markers of inflammation and oxidative stress. We may also genotype the DNA in the blood samples, however this genotyping will be limited to genes associated with air pollution exposure. We may also isolate RNA from cells recovered from the bronchoscopy and the blood for genetic analysis to see if there is a genetic difference between the after air and after chlorine exposures.

All fluid samples will be labeled with a study subject number that does not include personal identification information and will be stored in a repository where only project members will have access to the samples. There is a need to store samples in such a repository because this will be an ongoing study where samples from subjects will be collected over an extended period of time. Storing of samples allows for all samples to be processed at the same time and also allows our scientist the opportunity to further study these samples with as yet unknown questions and techniques.

How will the specimen be collected?

Venipuncture

The medical station staff will draw less than 3 fluid ounces of blood before exposures, immediately after exposure and 18 hours after the exposure.

Exhaled breath condensate

. You will be asked to breath for 10 minutes, into a condenser. Exhaled water vapor and protein are frozen inside a disposable sampling cup contained within the counter-current cooling chamber of this device. You will perform this test before exposures, after the exposures, and the morning of the day following the exposures.

Nasal Lavage

After observing a demonstration of the delivery technique, you will spray a total of 4 milliliters of saline (less than a teaspoon) into each nostril using a hand held nebulizer that delivers 100 microliter/actuation (spray). Each lavage consists of eight sets of five sprays; you will blow your nose into a specimen cup immediately after each set of five sprays. The entire procedure should be completed in approximately 10 minutes.

Bronchoalveolar Lavage (BAL) and Brush Biopsy

You will undergo bronchoscopy the morning of the day following the both the chlorine and clean air exposures. Bronchoscopy is frequently used in the diagnosis of lung disease in both

Initial/Date _____

adult and pediatric patients. The procedure has also been used in numerous research studies of persons with respiratory disease and in healthy volunteers. The procedure has been used safely many times in studies conducted at our laboratory. The purpose of the BAL procedure is to obtain fluids and cells from the lower regions of the respiratory tract, i.e., the trachea, bronchi and smaller airways. These materials will be analyzed to obtain information about the role of various chemical substances and cells in the pulmonary response to inhaled chlorine gas The bronchoscope is a highly flexible fiberoptic tube that is two feet long and about 1 centimeter in diameter (about the diameter of a pencil). It is an optical device with a light at the end which can be used to transmit images to a camera connected at the other end. Using the bronchoscope, the physician can see into your airways and direct the placement of the bronchoscope. A small channel allows fluid to pass through the bronchoscope.

The BAL procedure will be performed at the laboratory medical station by trained experienced pulmonary physicians. You will be expected at the medical station at 8:00 on the morning after the exposure. If you have had anything to drink or eat since midnight the night before the bronchoscopy you will not be allowed to proceed. You may terminate the bronchoscopy procedure at any time. If the physician deems that you are too uncomfortable or anxious, the procedure will be terminated.

A saline lock will be placed in a vein in your arm (a saline lock is a small catheter that stays in your arm for a short time) and will remain in place so that it can be used to administer medications in case there are any problems during the procedure. You will also be connected to a telemetry monitor that will display heart rate and rhythm, a blood pressure cuff will be placed on your arm, and an oximeter sensor (small band like device) will be placed on a finger to allow the medical staff to monitor you during the procedure. No sedatives and/or narcotics will be administered at any time during bronchoscopy. Atropine may be used at the discretion of the physician; this medication is used to suppress airway secretions and to prevent low heart rate.

Before proceeding, the medical staff will again make certain that you have had nothing to eat or drink since midnight the previous night. They will then give you a lidocaine solution and ask you to gargle with it for a few seconds to anesthetize your throat. You will then be asked to inhale (snort) a small amount of lidocaine jelly through one nostril to anesthetize your nose and the back of your throat. A Q-tip with lidocaine jelly will be gently inserted into your nose to ensure that your nose is completely numb before the bronchoscope is inserted. The procedure will not begin until your nose and throat are well anesthetized. If this cannot be accomplished, the bronchoscopy will not be performed. A tube delivering oxygen will be placed inside your other nostril. Delivery of supplemental oxygen is done as a precaution during all bronchoscopies conducted at our facility.

To start the procedure, the physician will pass the bronchoscope through your anesthetized nasal passage to the back of your throat and then to above your vocal cords. He will then inject a lidocaine solution to numb your vocal cords before passing the bronchoscope into your trachea (windpipe). More lidocaine, up to a safe maximum dose is injected at various points in your trachea and airways to minimize coughing during the procedure. You will experience some cough during the procedure. This is a normal reflex caused by the presence of the bronchoscope in your airway. The bronchoscope will be gently wedged in an airway in the right lung and sterile saline will be injected in your lung through a channel in the bronchoscope. The saline will then be gently suctioned from your lung through the channel in the bronchoscope. This sequence will constitute a wash. Six (6) washes will be performed. A total of 270 cc (about one-half pint) of sterile saline will be used during the BAL procedure. Approximately 75% of the saline

Initial/Date _____

injected into your lungs will be recovered by aspiration (suction) through the bronchoscope. The remaining 25% (75 cc) is expected to remain in your lungs. The saline left in your lungs should not cause any difficulty breathing or harm you and will be completely absorbed by your lungs within 48 hours.

After the BAL is performed, brush biopsies of your airway epithelium will be taken. A very small brush will be inserted through the channel in the bronchoscope. The brush is visible to the physician performing the procedure through the bronchoscope. Small amounts of surface cells are scraped from the airway by gently brushing the airway several times. Two (2) brush biopsies are taken at one site in the left. After the brush biopsies are obtained, the procedure will be complete and the bronchoscope will be removed from your airway. The total time the bronchoscope will reside in your airways will be 10-20 minutes.

After the procedure the oxygen cannula will be removed if your oxygen saturation is acceptable. Similarly, the chest electrodes will be removed if your heart rhythm is normal. The nurses will check your vital sign immediately after the procedure and one half hour, one hour, and 1.5 hours thereafter. During this time you will sit in a recliner at the medical station for an observation period of an hour. You will not have any food or drink during this time. After the recovery period, the nurses will check your gag reflex. Since the gag reflex will be absent due to anesthesia during the procedure, you will not be allowed to eat or drink until the anesthesia wears off. This normally takes about one to one-and-one half hours. Once your gag reflex returns, you will then be given some juice to sip and then some crackers.

The physician who performed the procedure will check you after the recovery period. You will be discharged if your vital signs are stable and chest examination is normal. Prior to discharge you will be requested to take 600mgm of ibuprofen by mouth; administration of ibuprofen/motrin almost always prevents the post-bronchoscopy malaise and low grade fever that would otherwise occur in about 25% of persons undergoing the procedure (acetaminophen/tylenol is a less effective alternative medication).

If you do not feel like walking, riding your bicycle, driving or taking the bus, the nurses will arrange to have a taxi take you home. The fare will be paid by the laboratory. Before going home, you will be give the phone number of the medical station (966-6232) and pager number to the physician who performed the bronchoscopy with instructions to call if you experience any adverse symptoms such as: 1) persistent fever or fever above 101 degrees Fahrenheit, 2) persistent cough, 3) sputum (phlegm) production, 4) chest pain, 5) coughing up any amount of blood, 6) nose bleeds, or 7) shortness of breath.

What will happen to the specimen?

Study samples will be stored in a secure room with restricted access at the U.S. Environmental Protection Agency Human Studies Facility located in Chapel Hill, North Carolina. The sample will be prepared, labeled with the study subject identification number, and stored indefinitely in a freezer for future testing. Names of subjects associated with ID numbers will be archived and locked; only medical and scientific personnel directly associated with this study will have access to this information. No personal identifying information will be attached to the biologic fluid samples. Portions of the samples may be shared with researchers at other scientific institutions, however, only coded samples will be sent. Under no circumstances will any identifying information be sent along with samples to outside investigators.

Initial/Date _____

What are the possible benefits to you?

Benefits to you are unlikely. These studies (current and future) may provide additional information that will be helpful in understanding of whether or how, exposure to low level chlorine gas affects people. Chlorine gas is identified as an air toxic by the U.S. Environmental Protection Agency and is regulated under the Hazardous Air Pollutants (HAPS) section of the Clean Air Act. The results of this study may ultimately play a role in regulation or standard setting for occupational or environmental exposure to chlorine and other respiratory irritants.

What are the possible risks or discomforts involved with being in this study?

This study might involve the following risks and/or discomforts to you:

1. **Blood sampling** will be performed by well-trained personnel, and entails only a risk of mild discomfort with the infrequent possibility of lightheadedness, fainting, infection or developing a bruise.

2. There are essentially no risks to performing the exhaled breath collection or nasal lavage.

3. There are several risks associated with performing **bronchoscopy,** although these risks are exceedingly small when bronchoscopy is performed on young healthy subjects, the type of people involved in this study. The primary risk of bronchoscopy is discomfort in the nose and throat, which is caused by having the bronchoscope inserted through the nose and passed through the back of your throat to reach the trachea (windpipe) and the airways leading to the lungs. This discomfort is alleviated with topical lidocaine, which you will gargle and inhale prior to the procedure. If you are suffering from discomfort in your nose and throat because they are not adequately anesthetized, you can request that more lidocaine be used, however, there is a limit to the maximum amount of lidocaine that can be given. If you are unable to tolerate the passage of the bronchoscope thorough your nose and throat because of pain in spite of having received the maximum allowable amount of lidocaine, the procedure will be immediately terminated.

A second risk of having bronchoscopy performed is coughing. Coughing is caused by irritation from the bronchoscope itself or the instruments used to obtain the biopsy material. Lidocaine liquid can be sprayed into your airways thorough the bronchoscope to relieve coughing. If the coughing is uncontrollable even with the use of the maximum amount of lidocaine, the procedure will be stopped immediately.

Lower airway bleeding can also occur from injury to the airway wall caused by the bronchoscope or the biopsy procedures. This bleeding is usually very minor (less than a teaspoon of blood). The bleeding resolves spontaneously within several minutes. If the bleeding is mild to moderate, epinephrine (adrenalin) can be sprayed on the bleeding site through the bronchoscope to hasten the clotting.

The **lidocaine** used for anesthesia during the procedure can have some adverse effects because some of the lidocaine can be absorbed into the blood stream from the nose and lungs. If you are allergic to lidocaine, you could develop itching, hives, difficulty breathing, and possibly shock (a dangerous drop in blood pressure). This risk is minimal, but you will be excluded from participating in this study if you are allergic to lidocaine or any other topical anesthetic that is commonly used in minor surgical or dental procedures. Lidocaine can also cause symptoms in your central nervous system (confusion, tremor, euphoria, or, rarely, seizures) or heart rate

Initial/Date _____

disturbances (very fast or very slow heart rate) if an excessive dose of medication is used. Finally, a death in a volunteer receiving an overdose (over 1000 milligrams) of lidocaine during bronchoscopy has been reported from Rochester, New York. However, no serious side effects of this medication have been noted at lower doses such as those described in this protocol which uses up to 360 milligrams of lidocaine during the entire procedure. If any problems develop secondary to the use of lidocaine, the physician bronchoscopist and the doctor on duty that day at the Human Studies Division of the EPA will be available to handle these problems.

Atropine, the medication that may be given to you by vein before the procedure starts, is given to help prevent your blood pressure and pulse from falling when the bronchoscope is first put into your airway, and to reduce the amount of secretions present in your nose, throat, and airways during the procedure. Atropine can cause you to have a dry mouth and nose as well as an increased pulse for about 30 to 60 minutes after it is given. These side effects are not harmful to you, and they wear off within 30 to 60 minutes after the drug is given.

The **placement of an IV catheter** in your arm can cause some pain. However, the IV is placed by a registered nurse who is very experienced in this technique, and the pain is very minor, usually resolving very soon after the IV catheter is in place. Rarely, placement of an IV catheter can result in the formation of a hematoma (bruise) at the site of the IV after it is removed. Also, a rare complication of IV placement is skin infection or an infection of the vein in which the IV catheter has been placed. The risk of getting an infection from the IV are minimized by the nurse's use of sterile technique of place the catheter. If you do have signs of infection at the IV site (redness, warmth, painful skin, swelling) after completion of the procedure, you will need to contact the EPA medical station (966-6232) or the physician who performed the bronchoscopy. You are not at increased risk by having blood drawn through the IV catheter.

Some subjects who undergo bronchoscopy have a low-grade fever (less than 101 degrees Fahrenheit) and experience symptoms of malaise and low energy after the procedure is completed. To prevent this from occurring you will be asked to take 600 mgm of ibuprofen (advil, motrin) before you are discharged from the medical station. This fever is almost always benign, occurs in approximately 25 percent of all subjects who undergo bronchoscopy, and is almost always prevented with the use of ibuprofen. Nevertheless, a persistent fever or any temperature of greater than 101 degrees Fahrenheit might mean that you have an infection, particularly pneumonia. Therefore, if you have any fever greater than 101 degrees Fahrenheit after the bronchoscopy or a fever that doesn't resolve in 24 hours after the procedure is completed, you should contact the EPA medical station or the physician who performed the bronchoscopy so that arrangements can be made for you to be examined by one of the physicians at EPA. You will be called 24 hours after the procedure to check on your condition. In addition, there may be uncommon or previously unrecognized risks that might occur. You should report any problems to the researchers.

4. **Risk of breach of confidentiality** is minimal. You will be assigned a study number which will be used for data – not your name. The study number is all that will be entered into computer databases. All paper files which may contain your name or screening number are secure in the EPA building which has limited access 24 hours/day. A numeric coding system will be used to ensure that you cannot be directly identified from the samples alone.

Initial/Date _____

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers

Will there be any cost to you for storage of the specimens?

There will be no cost to you for the storage and use of the specimens for research purposes.

Will you receive anything for being in this study?

You will be receiving $12.00 per hour for taking part in this study plus additional incentives for preforming procedures which produce discomfort (venipuncture $20, nasal lavage $20, bronchoscopy with BAL $350). You will be paid a bonus of $25 for arriving on-time on the two exposure days. You will be paid the same whether or not the follow-up methacholine challenge is required. You will also be paid a completion bonus of $125 for completing all parts of the study. A detailed break-down of the payment schedule and time requirement is as follows:

Procedure	Time	Payment
Training	4 hr	$ 48
Chamber exposure (9 hr)	18 hr	$ 216
BAL Day Testing (2hr)	4 hr	$ 48
F/U Methacholine Challenge	2 hr	$ 24
6 Venipuncture ($20 each)	N/A	$ 120
7 Nasal lavages ($20 each)	N/A	$ 140
2 bronchoscopies ($350 each)	N/A	$ 700
2 On-time bonuses ($25 each)	N/A	$ 50
1 Completion bonus ($125)	N/A	$ 125
TOTAL :		$1471

It is expected that if you undergo the training, the two exposures and bronchoscopy days and the follow-up day with the called for venipunctures, and bronchoscopies and qualify for the completion bonus, you will receive a total payment of $1471. If you complete the dry run at the beginning of the study, you will be paid an additional $148. You will be paid a nominal fee to offset transportation expenses if you travel from outside the Chapel-Carrboro area, and parking will be provided. All payment will be made at the end of the study unless a specific request for prior partial payment is made by the subject.

You understand that your participation is voluntary. You may terminate your participation in the study at any time without penalty, and without losing benefits to which you would otherwise be entitled. If you elect to terminate your participation in the study, you will be paid for that portion of the study which has been completed. The investigators also have the right to stop your participation in the study at any time. If you develop an illness or injury that precludes you from further participation in the study you will be paid for the portion of the study you have completed.

Payments totaling more than $600 in a year from a single or multiple EPA studies will be reported to the IRS.

Initial/Date _____

Who owns the specimens?

Any blood, body fluids, or tissue specimens obtained for the purpose of this study become the exclusive property of the U.S. Environmental Protection Agency. The researchers may retain, preserve or dispose of these specimens and may use these specimens for research that may result in commercial applications. There are no plans to compensate you for any future commercial use of these specimens.

How will your privacy be protected?

You will be assigned a study identification number. Names of subjects associated with ID numbers will be archived and locked; only medical and scientific personnel associated with this study will have access to this information. No personal identifying information will be attached and/or recorded in the data log sheets, biologic samples, or electronic data sets. No subjects will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, the U.S. Environmental Protection Agency and UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

Study samples will be stored in a secure room with restricted access. The sample will be prepared and stored indefinitely in a freezer for future testing. Portions of the samples may be shared with researchers at other scientific institutions, however, only coded samples will be sent. Under no circumstances will any identifying information be sent along with samples to outside investigators. All medical records generated during this study will be kept in the medical records office at the EPA Human Studies Facility. The Medical Station is locked when not attended by study staff, and the EPA Human Studies Facility has limited access to authorized individuals only, 24 hours/day for 7 days/week.

Will researchers seek approval from you to do future studies involving the specimens?

By signing this consent form, you are giving your permission for researchers to use your specimens as described above. Current and future research is overseen by a committee called the Institutional Review Board (IRB). The role of the IRB is to protect the rights and welfare of research participants.

In some cases, the IRB may require that you be re-contacted and asked for your consent to use your specimens in a specific research study. You have the right, at that future time, not to participate in any research study for which your consent is sought. Refusal to participate will not affect your medical care or result in loss of benefits to which you are entitled.

Will you receive study results of future research involving your specimens?

Most research with your specimens is not expected to yield new information that would be meaningful to share with you individually. In rare cases, you may be offered the opportunity to receive information about the results of research in which the specimens were used (for example, findings that would affect your medical care).

Initial/Date _____

Can you withdraw the specimens from the research study?

If you decide that you no longer wish for the specimens to be stored, you should contact the researchers on the front page of this form. You may also contact the Institutional Review Board, University of North Carolina at Chapel Hill, 919-966-3113, Medical School Building 52, CB 7097, Chapel Hill, NC 27599, or by email at IRB_subjects@unc.edu. It is best to make your request in writing.

Any analysis in progress at the time of your request or already performed prior to your request being received by the researcher will continue to be used as part of the research study. Once the researchers have been notified, your specimens would be destroyed. If you do not make such a request, the specimens may be stored forever. The researchers may choose to destroy the specimens at any time.

What will happen if you are injured by this research?

All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from having your specimen collected. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care. If you believe you have suffered a research-related injury, you have the right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

Who is sponsoring this study?

This research is funded by the United States Environmental Protection Agency. Several of the investigators including the Principal Investigator are federal employees. The researchers do not, however, have a direct financial interest in the final results of the study.

What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, you should contact the researchers listed on the first page of this form.

Initial/Date _____

What if you have questions about your rights as a research subject?

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously, if you wish, the Institutional Review Board at 919-966-3113 or by email to IRB_ subjects@unc.edu. You may also contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217.

Subject's Agreement:

I have read the information provided above. I have asked all the questions I have at this time. I voluntarily agree to participate. I agree to my specimen(s) being stored with the identifying code(s).

_____ _____

Signature of Research Subject Date

_____

Printed Name of Research Subject

_____ _____

Signature of Person Obtaining Consent Date

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Printed Name of Person Obtaining Consent

Initial/Date

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